REMARKS

Claims 11-22 currently appear in this application. The Office Action of July 21, 2004, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicants respectfully request favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Interview Report

Applicants' attorneys wish to thank Examiner Kishore for the courtesies extended to them and to Professor Barenholz during the personal interview of September 15, 2004. During that interview, claims 1-10 were discussed with respect to the cited references, namely, U.S. Patent 6,696,080, Hamaguchi U.S. Patent 4,844,904, Schneider, U.S. Patent 5,626,832, Legros, U.S. Patent 5,244,678, and Kirby, *Biotechnology*, 1984.

Professor Barenholz tendered a declaration demonstrating that it is critical when preparing liposomes according to the present invention that the liposomes be washed with hyperosmotic saline to reduce the liposome size and provide a higher than expected concentration of the drug. Examiner Kishore pointed out that the declaration did not specify what was the morality of the hyperosmotic solution.

However, the specification as filed at page 6, paragraph 0016, defines a hyperosmotic saline solution as one having a concentration of about 300 to about 600 mM NaCl. It was noted that the declaration established not only better stability, but, unexpectedly, one obtains a much higher load of anesthetic per milliliter using the present method.

The Examiner stated that the claims should be limited to bupivacaine. However, the specification as filed at page 14, paragraph 0034, indicates that the other "caines" have similar physicochemical properties to bupivacaine and can also be used in the present invention. Submitted herewith is information on the "caine" drugs showing their common properties.

Double Patenting

Claims 4-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of Bolotin et al., U.S. Patent No. 6,696,080 in view of Hamaguchi and Schneider.

This rejection is respectfully traversed. The patented claims are said to recite a method of preparation which is similar to the instant claimed method, differing only in the final washing step. Hamaguchi is said to disclose liposomal formulation in which the osmotic pressure of the

external phase is at least 20 percent more than the osmotic pressure of the solution used for entrapping the drug in liposomes. Schneider is said to teach that it is possible to use hypertonic solutions containing salts and glucose as the external medium.

This rejection is respectfully traversed. Claims 4-10 have been cancelled and replaced by new claims 11-22. New claims 11-22 make it clear that the last wash step is with hyperosmotic solution, which hyperosmotic solution is 300 mM to 600 mM saline. Submitted herewith is the declaration of Yechezkel Barenholz demonstrating that it is critical when preparing liposomes according to the present invention that the liposomes be washed with hyperosmotic saline (about 300 to 600 mM) in order to reduce the liposome size and provide a higher than expected concentration of drug. The Examiner concedes that Bolotin et al. do not wash with hyperosmotic saline. Hamaguchi et al., however, disclose dispersing liposomes obtained by removal of a solvent from a drug-containing water in oil emulsion in an aqueous solution having an osmotic pressure higher by at least 20 percent than the osmotic pressure of a solution used for entrapping the drug in the liposomes. Hamaguchi attributes the stability of the capsules (after four days) to the fact that the osmotic pressure of the bulk solution at liposome preparation relative

to the osmotic pressure of the dispersion. Schneider et al. do not add to the disclosure of Bolotin et al. and Schneider et al. merely disclose that hypertonic solutions containing one or more substances selected form salt glucose, opacifying agents, buffering agents, etc. There is no clear direction to use a hyperosmotic saline solution.

Since Bolotin et al. use water for the final washing, there is no reason to wash with saline solution. Schneider et al. and Hamaguchi et al. use saline for different purposes, Schneider et al. use solutions which are compatible with the living tissues and the liquids of the circulatory system, and Hamaguchi et al. to control the osmotic pressure in the liposomes relative to the solution used for entrapping the drug within the liposome.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Legros in view of Kirby. The Examiner admits that Legros prepares liposomes by the conventional methods, although it is disclosed that the liposomes can be prepared by any known art methods. Kirby merely discloses a method of preparing liposomes by dehydration-rehydration.

This rejection is respectfully traversed. Legros discloses that liposomes can be prepared by any method known in the art. However, at the time Kirby was published, 1984,

the method of preparing liposomes by dehydration-rehydration and then washing with hyperosmotic saline solution of 300 mM to 600 mM concentration was not a conventional method. There is thus no reason for one skilled in the art to produce liposomes by other than the dehydration-rehydration method. There is neither disclosure nor suggestion of using hyperosmotic saline of 300 to 600 mM concentration for a final wash of the liposomes.

Professor Barenholz has demonstrated in the declaration submitted herewith, that the wash with hyperosmotic saline is critical when preparing liposomes. Liposomes washed with normal saline solution had 12.90 mg bupivacaine/ml (36.0 nmol phospholipid/ml), while the same liposomes when washed with normal saline followed by a final wash with hyperosmotic saline, resulted in 25.9 mg bupivacaine/ml (95.5 nmol phospholipid/ml). It is clear that the final wash with hyperosmotic saline as defined in the present application produces liposomes which have a higher concentration than liposomes prepared the same way without the hyperosmotic saline wash.

Submitted herewith is a copy of pages 1-14 from Doctor Spiller.Com, a web site of a dentist, discussing local anesthetics, including the "caine" compounds. It should be

noted on page 3, "Over the next thirty years, a number of other amide local anesthetics were invented, most not differing significantly from lidocaine. Note on page 6 that it is noted that all local anesthetics are weak bases. Note on page 10 that the pKa of the "caine" compounds is within a rather small range, 7.6 to 9.1.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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